(a) identifying the repeat sequence in the cassette array;

A1

(b) hybridizing oligonucleotide primers to repeat sequences and amplifying the DNA between the primers to produce DNA fragments which contain one or more genes; and

(c) ligating the DNA fragments into a vector for cloning the on or more genes in a host cell.

2. The method of claim 1 wherein the one or more genes are selected from the group of peptides consisting of: adhesins, pilus proteins and outer membrane proteins; transporter peptides; toxins; hemolysins; hemagglutins; signaling peptides; detoxifying enzymes; catabolic enzymes specific for compounds episodically available, excluding compounds in the tricarboxylic acid cycle; and enzymes for biosynthesis of rare sugars, excluding ribose, deoxyribose; and sugars of the cell wall and the pericellular envelope.

A2

18. The method of claim 2, wherein the adhesins are fimbrial proteins.

19. The method according to claim 2, wherein the signaling peptides are kinases.

A2

20. The method according to claim 2, wherein the detoxifying enzymes are drug resistance determinants.

A marked-up version of claim 1 is attached hereto.

REMARKS

Claims 1-2 have been amended and claims 18-20 have been added. Applicants acknowledge with appreciation the allowance by the Examiner of claims 7-14 and 17. No new subject matter has been introduced. Support for the amendments in claim 1 may be found on page 15. The amendments have been made for purposes of clarity.

Claims 2 is rejected under 35 U.S.C. §112 second paragraph as indefinite. Phrases "such as", "especially", "small molecule", "narrow" have been amended are requested by the Examiner for purposes of clarity.

Rejection under 35 U.S.C. §102(b)

Claims 1,2,5 and 6 are rejected as anticipated by Silver et al. citing Figure 4, step 1, Figure 4, step II and III, column 7 lines 13-17, column 8, lines 26-28, Figures 1-4, col 6 lines 61-68.

The Silver reference is entitled: "DNA amplification technique" and is directed to analyzing sequences flanking any randomly sequenced stretch of DNA. The abstract states:

> The method allows the amplification of regions of DNA flanking a single region of known sequence in contrast to standard PCR which requires two regions of known sequence at opposite ends of the fragment to be amplified. (emphasis added)

Unlike the Silver reference, the present claimed method may be achieved by standard PCR because cassette arrays are characterized by genes embedded in a predictable sequence context so that amplification can occur between opposite ends of the fragment to be amplified.

> Indeed, the present claimed method requires step (b) hybridizing oligonucleotide primers to repeat sequences and amplifying the DNA between the primers to produce DNA fragments which contain one or more genes

The significance of the Silver reference appears to be that it is possible to amplify regions of DNA for which only a single adjacent sequence is known. Silver et al. achieves this by using restriction endonucleases that cut the DNA within the unsequenced region and within the sequenced region, permitting the subsequent DNA to be ligated and subsequently amplified.

According to the Silver et al. reference, ligation precedes amplification. However, the present claimed invention requires amplification to precede ligation.

Moreover, the use of restriction endonucleases by Silver et al. is quite different from embodiments of the claimed method (claim 3) which describes a method for cloning restriction endonucleases.

There is no literal or inherent suggestion in Silver et al. for cloning a gene which is embedded in a predictable sequence context including a repeat DNA sequence.

If a person of ordinary skill in the art were to utilize the Silver reference, they could not deduce or achieve the method of the present claims. For example, in the method of amplification in column 3, line 58-column 4, line 10, ligation is required to

precede amplification (also see Figure 4 steps I-III). This requirement is contrary to the present claimed method as is clear from element (b) and (c) of claim 1. Moreover, the Examiner states that Figure 4 step (I) teaches element (a) of the claimed method which requires identifying repeat sequences. However, Figure 4 (I) describes CC.....unknown sequence. CC is a not a repeat sequence because a single nucleotide is not a sequence. Moreover, although the LTR (long terminal repeat) is part of the known sequence of the provirus, the unknown sequence is not embedded in the LTR which is why Silver et al. is unable to use standard PCR methods which are useful for the claimed method. Figure 4 (II) and (III) show why Silver et al. must ligate the unknown and known sequence into a circular plasmid prior to amplification. As stated above, the present claimed method requires that amplification precede ligation, a requirement that appears not to be possible in the Silver reference.

The Examiner has recited col 6, lines 61-69 which exemplify "inside-out" PCR for amplifying unknown cell DNA on either side of a known provirus DNA. The provirus was selected because its sequence is known and because there are only a few such proviruses in mouse strains. There is no suggestion in this citation, inherent or otherwise, and no expectation of success in applying the cited method for analyzing an unknown cell DNA environment for a murine provirus to cloning one or more genes

in a cassette array using flanking repetitive sequences as hybridization targets for primers.

The Examiner has cited column 7, lines 13-17 as anticipating element (b) of the method of claim 1. This citation describes introducing cleavage sequences for particular restriction endonucleases into target DNA to facilitate the cloning of junction fragments for amplification and sequencing to discover cellular sequences neighboring the provirus. As described above, this does not appear to relate to the claimed method which relies on identifying repeat sequences in the cassette array for targets for primers and the amplification of sequences therebetween and subsequently ligating the amplified fragments.

The Examiner has cited 13-17, column 8, lines 26-28 which describes purification and subcloning of a junction fragment for sequencing. As described above, this does not appear to relate to the claimed method which relies on identifying repeat sequences in the cassette array for targets for primers and the amplification of sequences there between for cloning genes

Rejection under 35 U.S.C. §103

The Examiner has rejected claim 3 as obvious in light of the Xu reference which describes an expression system in bacterial cells in view of Silver et al. As asserted above, Silver et al. describes a separate and distinct method from the claimed method for the reasons provided above. For the same reasons, the combination of Silver et al. with Xu who describes an expression system does not teach or suggest the present claimed method.

The Examiner has rejected claim 4 as obvious with respect to Stein in view of Silver et al. For the reasons given above, the claimed method is separate and distinct from the cited art.

For the reasons set forth above, Applicants respectfully request that the rejections set forth in the Official Action of August 12, 2002 be withdrawn and submit that this case is in condition for immediate allowance. Early and favorable consideration leading to prompt issuance of this Application is earnestly solicited. Applicants petition for an extension of three months under 37 C.F.R. 1.136 and enclose a check for $435.

Should the Examiner wish to discuss any of the remarks made herein, the undersigned attorney would appreciate the

The PTO did not acknowledge the following listed item(s) A check of $435.00 but we got $460.00.

opportunity to do so. Thus, the Examiner is hereby authorized to call the undersigned collect at the number shown below.

Respectfully submitted,

NEW ENGLAND BIOLABS, INC.

Date: 12/5/02

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